REMARKS

Upon entry of the amendments submitted herein, claims 32-47 remain pending in the application. Of these, claims 32, 37, 42 and 44 have been amended herein.

In the first place, Applicants acknowledge with gratitude the time taken by Examiners Kunz and Landsman to participate in a telephone interview with their agent to discuss the outstanding issues; the Examiners' input was much appreciated. Applicants also acknowledge Examiner Landsman's additional input during follow-up exchanges with their agent. The amendments and remarks herein are reflective of the agreement reached on the various issues during the course of the interview and follow-up exchanges.

In response to the maintained rejection of claims 32-47 in section 2B of the Office Action, claims 32 and 37 have been amended by replacement of the term "constituting" with the term "comprising."

With respect to the objection to the specification set forth in section 3A of the Action, the Sequence Listing itself has been amended to include the sequences appearing in Table 1 on page 15 of the specification. Similarly, the sequences appearing in Table 2 on pages 20 and 21 and the sequence on page

25, line 29 of the specification have been added to the Listing. In accordance with 37 CFR §1.821(d), the specification has been amended where these additional sequences appear by addition of the assigned identifiers from the Sequence Listing. A paper copy of the revised Sequence Listing is enclosed with this response. The computer readable form of the revised Sequence Listing is being submitted concurrently herewith to Mail Stop Sequence, as required.

As set forth in section 4A, claims 37-47 remain rejected under 35 USC §112, first paragraph on the grounds that the phrase "functionally equivalent modified variant" is not enabled. In the first place, as pointed out to the Examiners during the interview, there is considerable enabling disclosure in the instant specification. For example, precise locations of crucial regulatory sequences such as initiator elements, GC-rich regions and cAMP responsive elements have been identified within the promoters (see, for example pages 13 and 14). Moreover, instant Examples 5 and 6 describe the production of promoter variants generated by effecting changes in the crucial "functional" transcriptional control elements; these changes result in reduction of expression. Thus, firstly, one of skill in the art would appreciate that variants could be made with substantial changes to regions other than these crucial ones

without substantially affecting promoter function. As a corollary, the skilled artisan would realize from the instant disclosure which regions of the promoter should be avoided in making modifications. In the instant specification, the phrase "functionally equivalent modified form" (amended in the claims to "functionally equivalent modified variant" at the Examiner's suggestion) is defined as being a nucleic acid modified from the original sequence that can bind transcription factors. By teaching where the transcription factors bind, Applicants have taught which regions can be modified and which must not be modified in order to maintain functionality of the variants.

In addition to these considerations, it was also pointed out to the Examiners that removal of the phrase "functionally equivalent modified variant" would not broaden the scope of the claims; the remaining "active fragments" would certainly not include such variants of the promoters as ones formed by such modifications as substitutions and insertions. The Examiners agreed that this is the case and indicated that amendment of the claims to more precisely define what is meant by "variant" would be favorably considered. Applicants' agent pointed out the disclosure on page 6, lines 6-11 of the specification; the Examiners indicated that addition of language based on this disclosure would be satisfactory. Claims 37, 42 and 44 have

been amended in this way. The written description rejection of the claims set forth in section 5A is also addressed by these amendments.

As set forth in section 4B, the claims stand rejected as being nonenabled for a second reason. The Examiner asserted that "there is no discussion in the specification, including guidance or working examples, that the promoter actually modulates GABA receptor expression, nor do the claims remedy this deficiency." As discussed in the interview, this assessment is in error. The specification, particularly Examples 1 and 2, provides thorough disclosure demonstrating that modulation of reporter gene expression by a test compound is indicative that said compound would also affect GABA receptor expression.

In summary (see Example 1), the putative promoter sequences were obtained as follows: Applicants started with genomic DNA known to contain the human $GABA_B$ receptor gene. This material was manipulated in various ways to obtain a plasmid, pAM364, wherein was cloned a fragment of the $GABA_B$ receptor gene. In order to localize the putative promoter within the gene fragment, the sequence of the fragment was screened for the presence of consensus sequences of known regulatory promoter

elements. On this basis, two putative promoters, designated SEQ NOs:1 and 2, were identified and isolated.

As described in Example 2, these putative promoters were fused to a reporter gene, in this case one encoding firefly luciferase. The promoter-reporter constructs were transfected into a mammalian cell line chosen because it expresses functional $GABA_B$ receptors, and the expression of luciferase was monitored. It was clearly shown in these studies that the luciferase gene was well expressed, thus establishing that SEQ ID NOs:1 and 2 are indeed promoter sequences. The use of genes such as that for luciferase as reporter genes is standard procedure for monitoring promoter activity. Given the source of SEQ ID NOs:1 and 2, there can be no question that these molecules, demonstrated to have promoter activity, are in fact GABA receptor promoters.

Applicants have thus met the criterion for patentability with respect to enablement of this aspect. One of skill in the art would not only find credible the assertion that test compounds modulating reporter gene expression would modulate GABA receptor gene expression but would expect such to be the case. Applicants have provided an efficient system for identifying candidate compounds; they are not required to show directly the effect on GABA receptor expression.

Although the Examiners agreed that there was sufficient demonstration that test compounds modulating reporter gene expression would also be expected to modulate GABA receptor expression, they nonetheless requested that additional language be inserted into the claims to make clear the connection between the claimed method and the identification of modulators of GABA receptor expression. In the interest of expedited prosecution of the application, appropriate language has been inserted into step (c) of claims 32, 37, 42 and 44.

As further pointed out to the Examiners during the interview, there have been many prior teachings, including issued patents, employing systems akin to the present one, systems comprising fusion of a promoter to an "unrelated" reporter gene. Such systems were said to demonstrate effectiveness of the promoter in expressing the gene product naturally associated with said promoter and said to be useful in screening for compounds effective in modulating expression of said gene product. Clearly, then, these assertions of what such systems demonstrate and of the screening utility of such systems have routinely been accepted as valid. Applicants direct the Examiners' attention to, for example, U.S. Patent Nos. 5,811,231 to Farr, et al; 5,914,233 to Mundy, et al; and 5,994,061 to Tam, et al.

The amendments to the claims and arguments set forth above with respect to the rejection leveled in section 4B are also responsive to the rejection set forth in section 6B.

It is Applicants' understanding, based on the interview, that the rejection set forth in section 6C of the Action will be withdrawn without amendment of the appropriate claims. As explained to the Examiners in the interview, the term "specific" has a defined meaning and this term should not be removed from the claims. The significance of the term can be found, for example, in the passage running from page 2, line 29 through page 3, line 4 of the instant specification.

It appears in section 6D of the Action that the Examiner is withdrawing the indefiniteness rejection of claim 37 but is nonetheless suggesting an amendment to make the claim clearer. In the first place, it is the "nucleic acid molecule" and not the "promoter element" that is selected from the group consisting of (i) and (ii). Thus, the suggested amendment would not be appropriate. Furthermore, it remains Applicants' belief that the language is clear enough as it presently stands. For example, the recitation that the variant is at least 95% homologous to SEQ ID NO: 1 or SEQ ID NO: 2 makes it clear that, in the Examiner's words, "both parts (1) and (2) comprise parts (i) and (ii)."

The rejection set forth in section 6E should have been made only in connection with claims 37-47, since claims 32-36 do not contain the language in question. In any case, claims 37, 42 and 44 have been amended by replacement of the phrase "consisting essentially of" with "comprising."

Section 6H is not a rejection per se; no section of the statute has been cited nor has any requirement been made for amendment of the claims. In any event, the issue raised therein was discussed during the interview and the Examiners agreed that it is, after all, clear from the claim language that the "functionally equivalent modified variant" of claim 42 must be at least 95% homologous to SEQ ID NO: 1 and that said variant of claim 44 must be at least 95% homologous to SEQ ID NO: 2. Accordingly, no amendment to claims 42 and 44 has been made in response to the issue raised in section 6H.

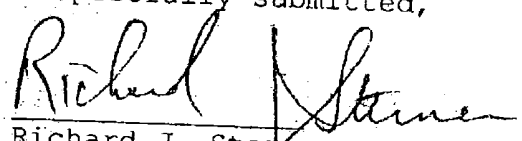
During the interview, all of the outstanding issues were discussed and it was either agreed that the issues were resolved without further amendment or agreement was reached on amendments that resolved the issues. The amendments and remarks herein address all of the outstanding issues in the way agreed upon during the interview. Accordingly, the application should be allowed; allowance of the application with pending claims 32-47 is respectfully requested. Should any other matters require

attention prior to allowance, it is respectfully requested that the Examiner contact the undersigned.

The Commissioner is hereby authorized to charge any additional fees which may be due in connection with this communication to Deposit Account No. 23-1703.

Dated: June 9, 2004

Respectfully submitted,



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Enclosure